Accurate prediction of response to HIV therapy without a genotype: a potential tool for therapy optimisation in resource-limited settings

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hiv resistance response database initiative

State of the ART

Key features of HIV treatment	Well-resourced settings	Resource-limited settings
Strategy	**Individualised**	**Public health**
Antiretroviral drugs	Approx. 25 from 6 classes	Limited availability / affordability
Diagnostic & monitoring tools	CD4, viral loads, resistance testing	CD4 (Viral load?)
Detection of failure	***Early*** – regular viral load monitoring	***Late*** – using CD4 or clinical symptoms
Salvage	Individualised – using genotype	Standard protocol – genotypes unaffordable
Expertise available	High & multidisciplinary	Mixed & thinly spread

Questions

- Can we enhance the long-term effectiveness of therapy in RLS?
- How do we get the best out of a limited range of drugs?

Previous studies using computational models

- Models predict response to therapy with approx. 80% accuracy:
  - Trained using data from many thousands of patients
  - Input variables: ***genotype***, viral load, CD4 count & treatment history[1,2]
- Models can predict response ***without a genotype*** with about 70-75% accuracy[3-5]
- At least comparable to the predictive accuracy of genotyping with rules based interpretation (62-69%)[6]

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Study objectives

1. To train models with a large global dataset including cases from RLS
2. To compare the accuracy of the models for patients from a global test set with those from southern Africa
3. To investigate if the models can identify alternative regimens for cases that failed in the southern Africa data set, using only those drugs available locally at the time

Model training

- **10 random forest models were developed:**
  - Training data: **22,567** cases of therapy change following virological failure (multiple sources, including 1,090 from southern Africa)
  - 43 input variables: viral load & CD4 count before treatment change, treatment history, drugs in the new regimen, time to follow-up & follow-up viral load
- **Output: prediction of the probability of response to therapy (<50 copies HIV RNA/ml)**

Assessment of model accuracy

- Cross-validation during training
- Independent global test set of 1,000 cases
- Independent southern African test set of 100 cases (sub-set of global set)

Main outcome measure - area under the ROC curve (AUC)

Secondary measures - sensitivity, specificity & overall accuracy, using the optimum operating point (OOP) obtained during cross validation

Cross validation

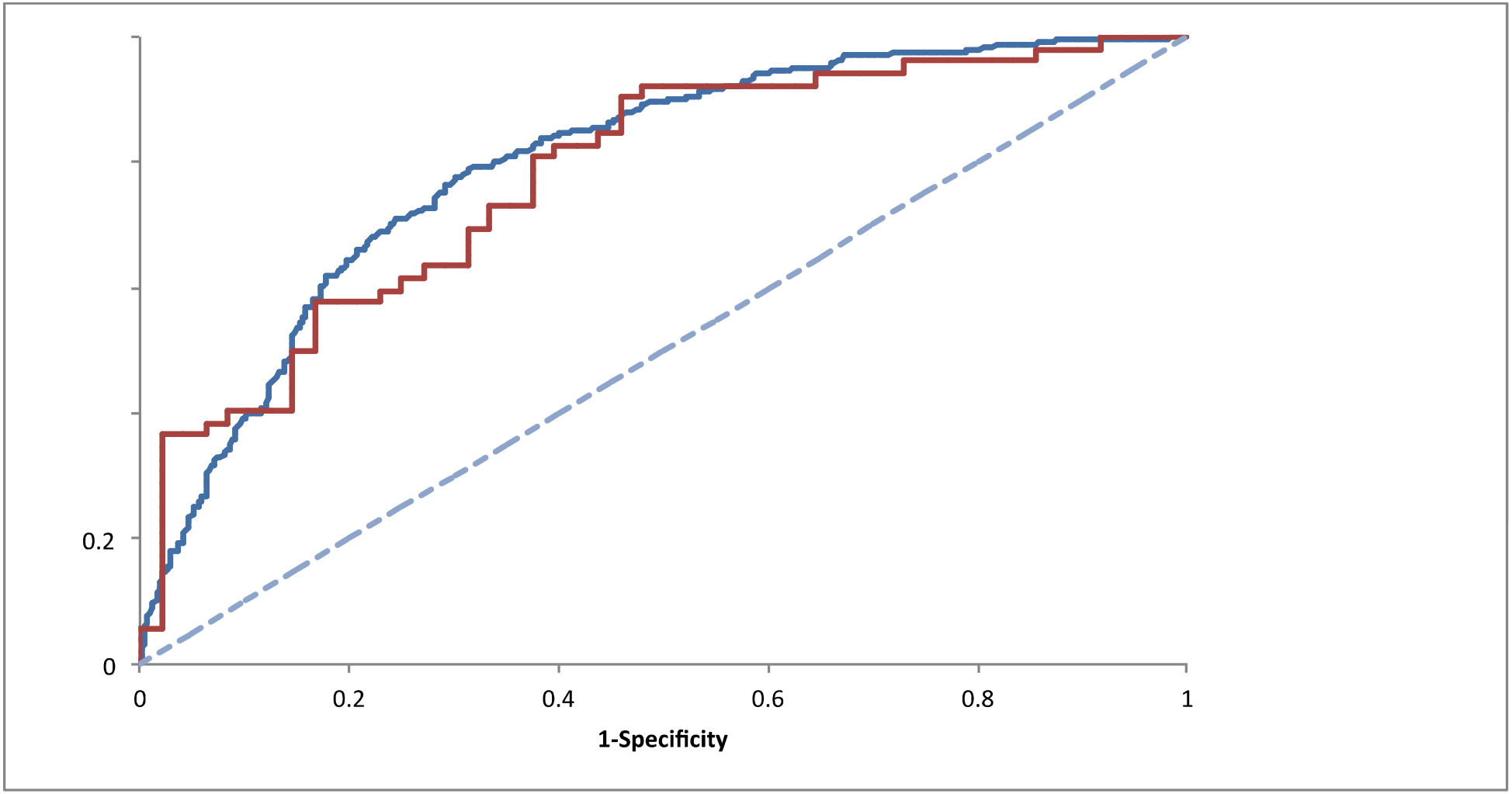
(10x, n = 22,567)

Model	AUC	Sensitivity (%)	Specificity (%)	Accuracy (%)	OOP
1	0.84	67	83	78	0.42
2	0.79	71	73	73	0.36
3	0.80	64	78	74	0.40
4	0.83	66	82	77	0.41
5	0.83	72	79	77	0.40
6	0.81	60	82	75	0.45
7	0.81	64	82	76	0.43
8	0.84	69	83	78	0.42
9	0.83	63	86	78	0.48
10	0.82	61	84	76	0.45
Mean	**0.82**	**66**	**81**	**76**	**0.42**
95% CI	[0.78, 0.85]	[58, 74]	[74, 88]	[73, 80]	[0.36, 0.49]

Independent testing

	AUC	Sensitivity (%)	Specificity (%)	Accuracy (%)
Global test set: n = 1000				
Ave	0.80	66	79	74
95% CI	[0.77, 0.82]	[61, 71]	[76, 82]	[71, 77]
Southern African cases: n = 100				
Ave	0.78	81	60	71
95% CI	[0.69, 0.87]	[67, 90]	[45, 74]	[61, 80]

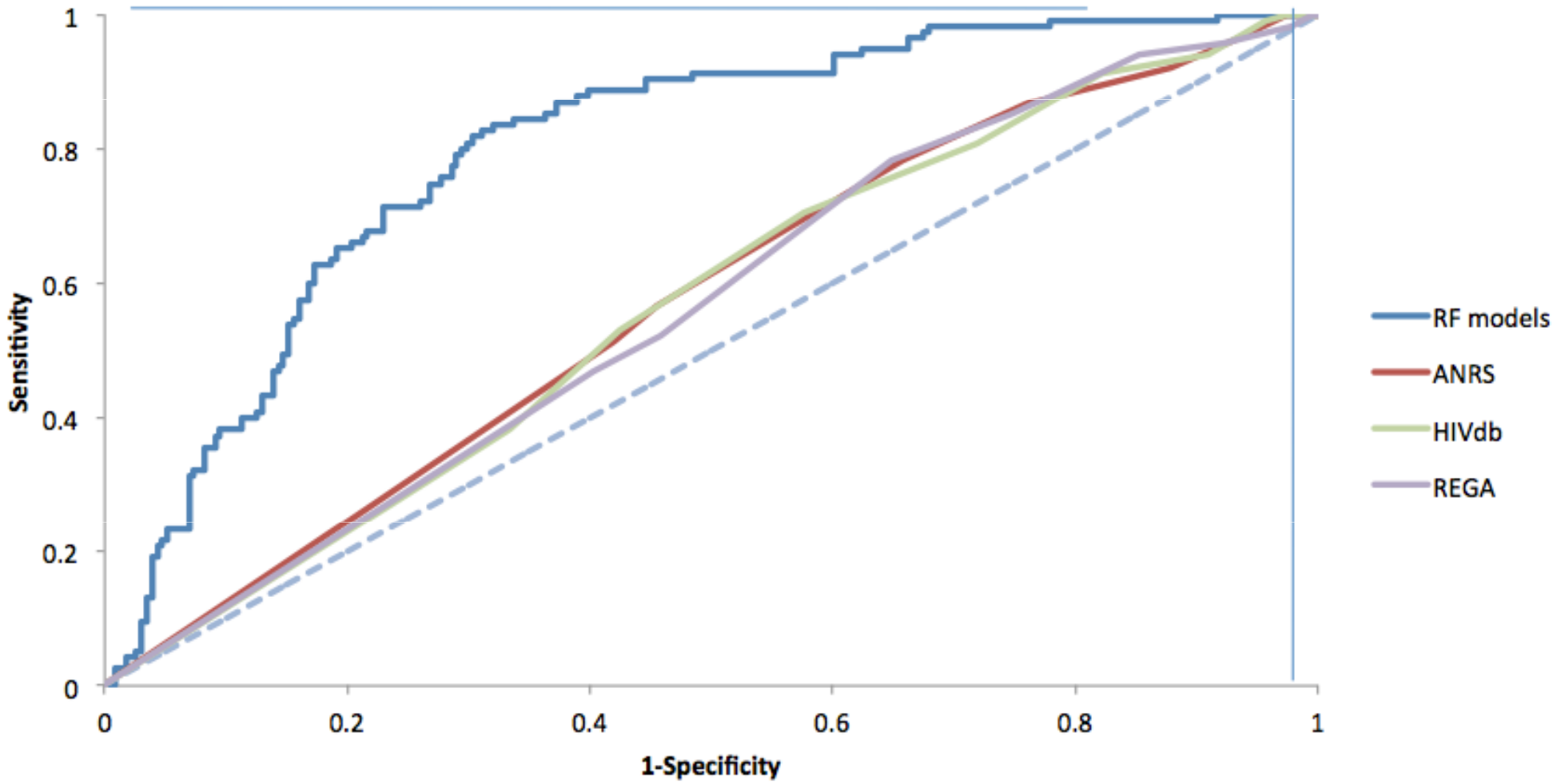
ROC curves



Comparison of models *vs* genotyping

- 346 cases used from global test set that had genotype available
- Total GSS (genotypic sensitivity scores) obtained separately using 3 rules-based interpretations systems (ANRS, REGA & Stanford HIVdb)
- Total GSS scores used as a predictor of virological response - accuracy compared to RF models (AUC)

ROC curves


1
0.8
0.6
0.4
0.2
0
Sensitivity
0
0.2
0.4
0.6
0.8
1
1-Specificity
RF models
ANRS
HIVdb
REGA

RF models *vs* genotyping

(346 cases from global test set)

		Sensitivity	Specificity	Accuracy	
Prediction System	**AUC**	**(%)**	**(%)**	**(%)**	***p*** **(GSS vs RF)**
ANRS	0.57	51	58	55	<0.0001
HIVdb	0.57	53	57	56	<0.0001
REGA	0.56	52	54	53	<0.0001
Ave:	**0.57**	**52**	**56**	**55**	
RF Models	**0.80**	**65**	**80**	**75**	

Modelling alternative regimens for southern Africa

- Baseline data from 100 southern African test cases input to RF models
- Predictions of the probability of response obtained for alternative 3-drug regimens comprising only those drugs available in the clinic at the time of the treatment change
- Outcome measure - the number of alternative regimens that were predicted to be effective

Modelling alternative regimens for southern Africa

	All cases (100)	Failures (n=48)	Correctly predicted failures (n=29)
Number (%) of cases for which alternatives were identified with a probability of response > OOP	76 (76%)	31 (65%)	12 (41%)
Median number of such alternatives	14.5	14	10
% cases for which alternatives were identified with a probability of response > than the regimen used	85 (85%)	46 (96%)	29 (100%)
Median number of such alternatives	7	9	16

Summary

- Models showed accuracy in the region of 80%
- Were comparably accurate for cases from southern Africa as for a global test set
- Were significantly more accurate than genotyping with rules-based interpretation (GSS)
- Identified alternative regimens that were predicted to be effective for the majority of cases where the new regimen used in the clinic failed

Overall conclusion

- **These models have the potential to help optimise therapy in countries with limited resources where genotyping is not generally available or affordable**

The new model are being made freely available via:

www.hivrdi.org/treps

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